The Human Genome Epidemiology Network (HuGE Net)

Muin J. Khoury, MD, Ph.D.

Director,
CDC Office of Genomics and Disease Prevention

"Welcome to the Genomics Era"
(NEJM Dec 2003)
"Genetic Testing for Sale"
Vineis, P, Christiani, D. Epidemiology Jan 2004

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Gene-Based Medicine in 2010?
"Hypothetical Genetic Test Report"

Condition	Genes	RR	Lifetime
Prostate Ca	HPC1, 2, 3	0.4	7%
Alzheimer's	APOE,FAD3,XAD	0.3	10%
Heart disease	APOB,CETP	2.5	70%
Colon Cancer	FCC4,APC	4.0	23%
Lung Cancer	NAT2	6.0	40%

CDC
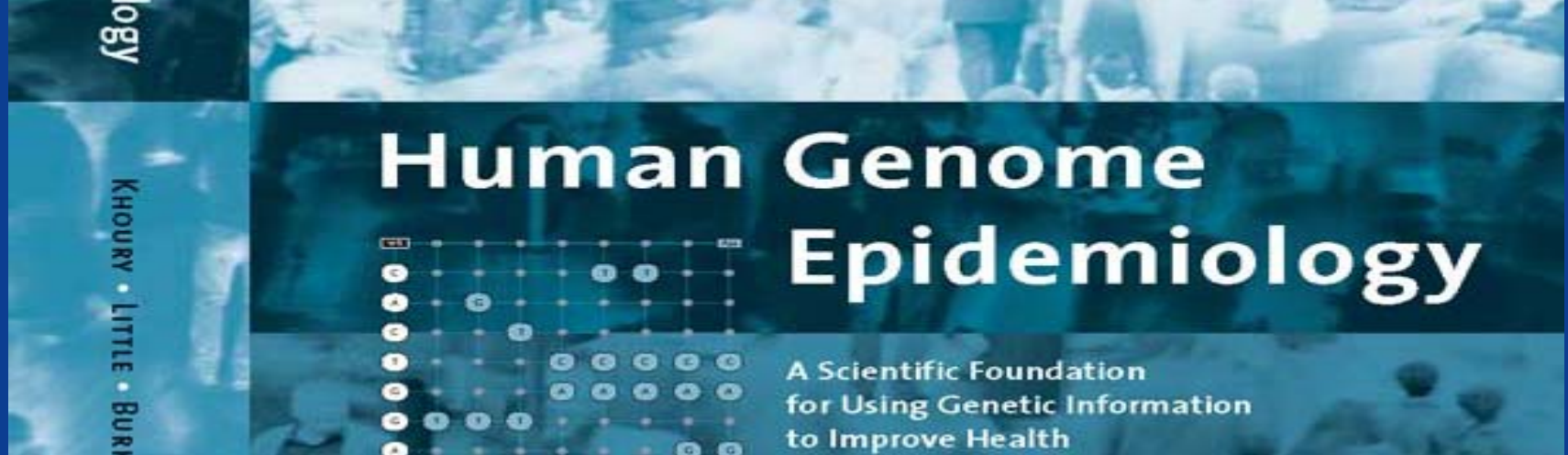
Human Genome Epidemiology

A Scientific Foundation for Using Genetic Information to Improve Health

KHOURY · LITTLE · BURKE

"Systematic application of epidemiologic methods and approaches to assess the impact of human genetic variation on health and disease"

Khoury, Little and Burke, HuGE 2004

- Genotype prevalence
- Gene - disease association
- Gene - gene interactions
- Gene - environment interactions
- Assessment of Genetic tests

Human Genome Epidemiology

A Scientific Foundation
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KHOURY · LITTLE · BURKE
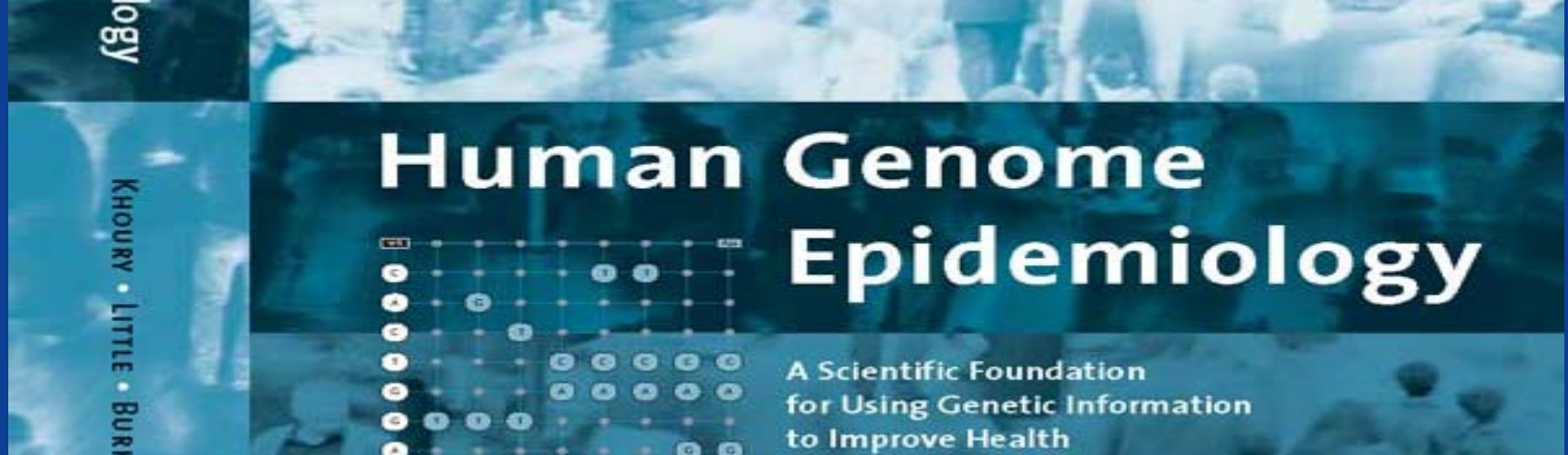
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Khoury, Little and Burke, HuGE 2004

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HuGE problem:
25,000 genes, their combinations and interactions with risk factors

CDC

The End of Black Box Epidemiology?

Risk Factors

Demographics

Diet

Occupation

Smoking

Alcohol

Environment
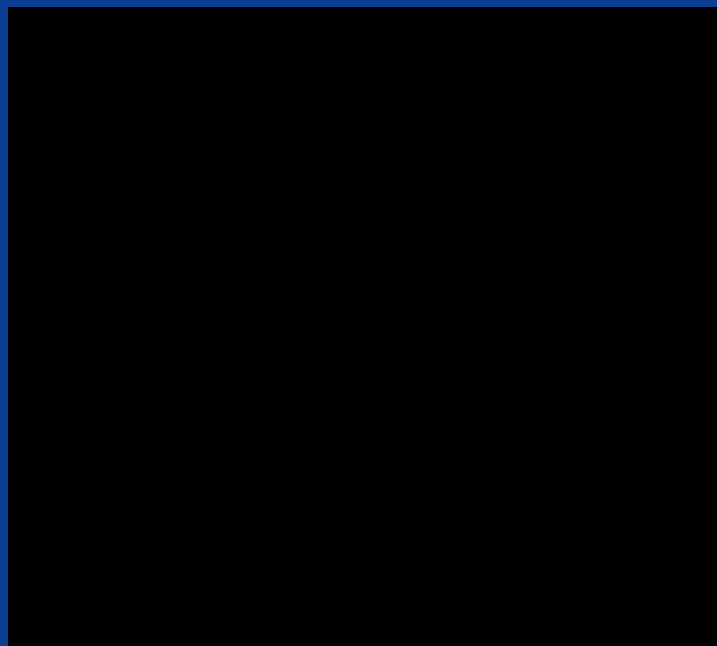
Adverse Health Outcomes

Activation of Maternal/Fetal HPA Axis
- Maternal-Fetal Stress
- Premature Onset of Physiologic Initiators

Inflammation
- Infection:
  - Chorion-Decidual
  - Systemic

Decidual Hemorrhage Abruption

Pathological Uterine Distention
- Multifetal Pregnancy
- Polyhydramnios
- Uterine abnormalities

Mechanical stretch

CRH E1-E3

Interleukins TNF-α Fas L

Prothrombin G20210A
Factor V Leiden
Protein C, Protein S
Type 1 Plasminogen
MTHFR

Gap jct
IL-8
PGE2
Oxytocin recep

CYP1A1 GSTT1

Chorion Decidua

+ CRH

Susceptibility to environmental toxins

proteases

+ MMPs

uterotonins

PROM

Cervical change

Uterine Contractions

Preterm Delivery

Courtesy S. Dolan MD

Adapted from: C. J. Lockwood, *Paediatr Perinat Epidemiol* 15, 78 (2001) & X. Wangl. *Paediatr Perinat Epidemiol* 15, 63 (2001)

From HuGE Research to Synthesis & Dissemination for Policy and Practice

Primary HuGE Research Agenda and Funding →

Study Design
Single studies
    (case-control,
    cohort
    biobanks)
Consortia

Implementation
    Candidate gene selection
    Risk factor data
    Outcome data

Identify
    Knowledge gaps
    Methodologic
    problems
    Research Priorities

Analysis: G-G, G-E

Interpretation
    Causal inference
    Risk estimation

Policy & Practice

Synthesis
    Reviews
    Meta-analysis

Appraisal
(Single study)

Dissemination

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HuGE Net

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Dissemination

CDC

Human Genome Epidemiology Network (HuGE Net)

- **Global collaboration of individuals and organizations to assess population impact of genomics and how it can be used to improve health and prevent disease (~700 collaborators, 43 countries)**
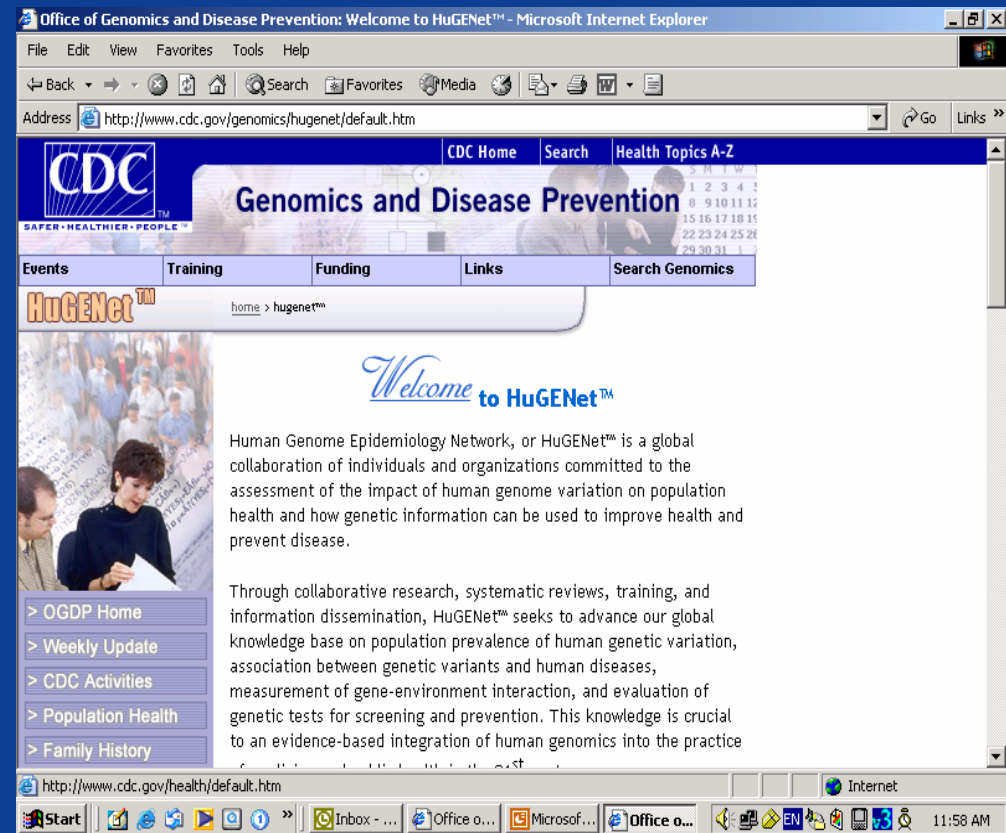
Human Genome Epidemiology Network (HuGE Net)

- Information Exchange
- Training and Technical Assistance
- Knowledge Base Development
- Information Dissemination
- Policy Development
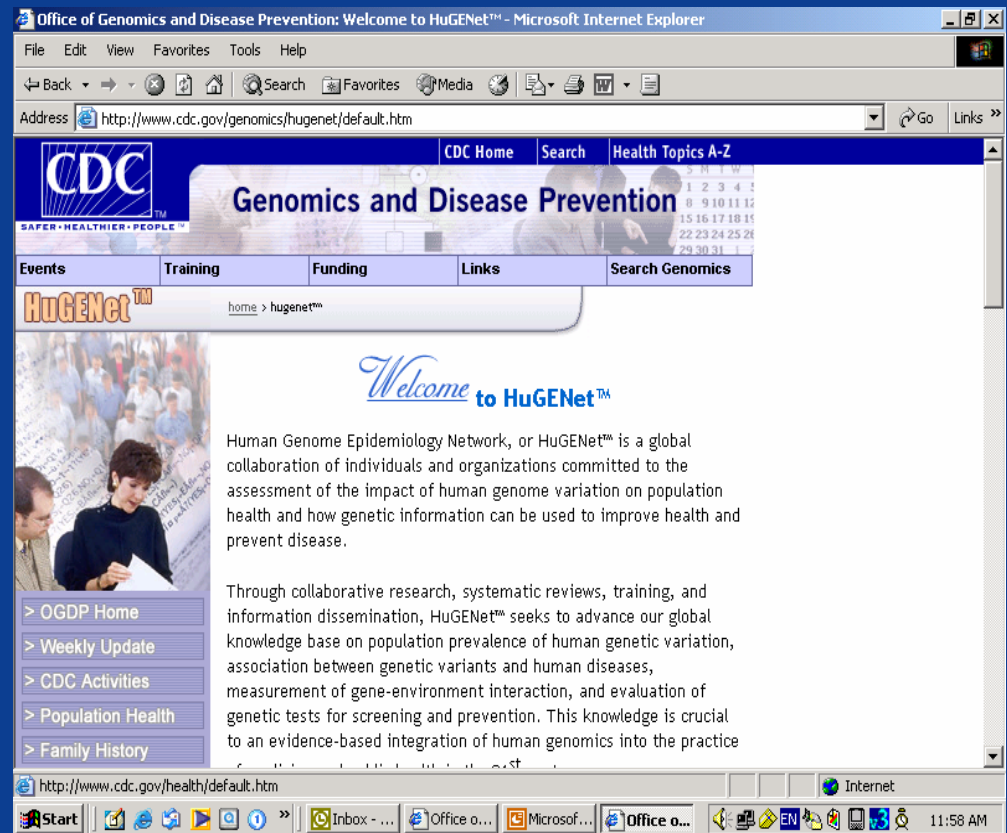
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HuGE Net

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Causal inference
Risk estimation

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HuGE
Meta-analysis

Policy &
Practice

Appraisal
(Single study)

Dissemination

HuGE Net Products
(as of January 10, 2005)

- **Reviews** 33
- **Fact sheets** 13
- **E-journal clubs** 53
- **Case studies** 4
- **Genotype Prevalence Database** 13
- **Methods workshop/guidelines** 2
- **Training workshops** 6
- **Book** 1

- **Published Literature Database** 14,127
  - **# Genes** 1710
  - **# Risk Factors** 559
  - **# Outcomes** 1797

CDC

HuGE Reviews
"Systematic Reviews of Gene-Disease Associations"

- Full Reviews
  - Abstract
  - Gene
  - Gene variants Prevalence
  - Disease/Health outcome
  - Associations
  - Interactions
  - Laboratory Tests
  - Population Testing and other applications
  - Recommendations for further research

- Mini-Reviews
- Gene-Disease Association Reviews
- Prevalence Reviews

HUMAN GENOME EPIDEMIOLOGY (HuGE) REVIEW

ERCC2/XPD Gene Polymorphisms and Lung Cancer: A HuGE Review

Simone Benhamou[1,2] and Alain Sarasin[2]

Figure 2:   Odds ratios for the relation between the *Asp / Asn* genotype of the xeroderma pigmentosum group D *Asp* 312 *Asn* gene polymorphism (vs. the *Asp / Asp* genotype) and lung cancer risk. For each study, the odds ratio estimate is plotted with a box; the area of each box is inversely proportional to the estimated effect's variance in the study. Diamond, pooled odds ratio; horizontal lines, 95% confidence interval.
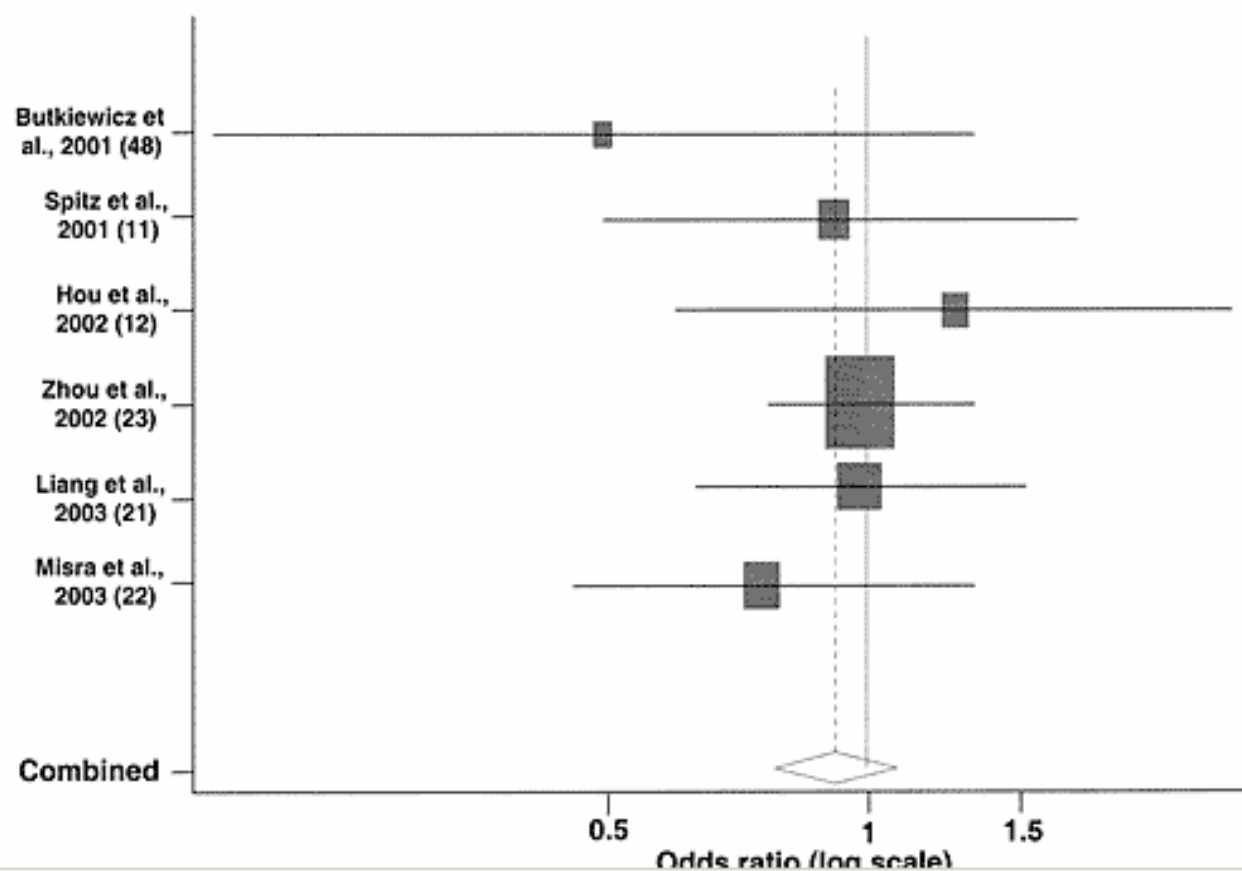
HuGE Reviews by Topic
Jan 10, 2005

- Cancer   13
- Cardiovascular   4
- Birth Defects   4
- Single Gene Ds   4
- Exposures   3
- Others   5

CDC

Systematic Reviews of Gene-Disease Associations: GDP Info: Oct 2000-Aug 2004

Category	Number	%
Cancer	34	23.9
Cardiovascular diseases	27	19.0
Mental Health	25	17.6
Neurologic diseases	12	8.5
Osteoporosis	6	4.2
Pregnancy/Reproduction	5	3.5
Infectious diseases (all HIV)	4	2.8
Diabetes	3	2.1
Autoimmune diseases	3	2.1
Obesity	2	1.4
Arthritis	2	1.4
Asthma	2	1.4

CDC

Genomics and Disease Prevention Information System (GDPInfo)

GDPInfo is a searchable database of documents available on the Office of Genomics and Disease Prevention's (OGDP) Web site as well as links to relevant documents on other sites.

GDPInfo Search

Try it! Search by

- Gene
- Disease
- Interactive Factor

What is in GDPInfo?

- fact sheets
- reviews
- case studies
- published literature
- online presentations
- books and book chapters
- materials from conferences and workshops

Why GDPInfo?

To provide access to information and resources for guiding public health research, policy, and practice on using genetic information to improve health and prevent disease.

Who Uses GDPInfo?

Public health professionals are the target audience but there are data and information for researchers, health care providers, and the general public.

http://www.cdc.gov/genomics

CDC

No. of articles in Huge Published Literature db, 2001-2004*
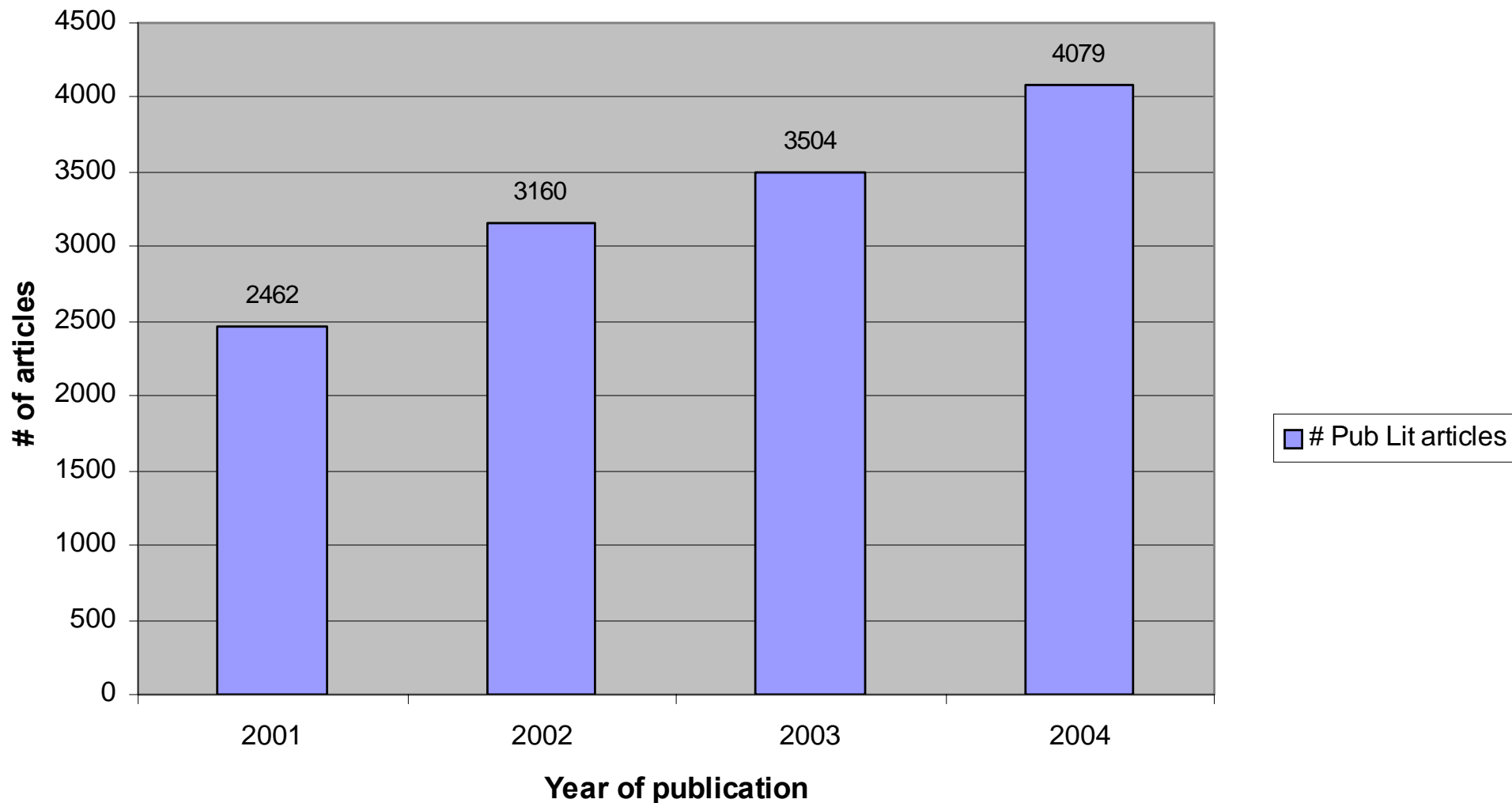
(*As of Jan 14, 2005. Count excludes review articles, meta & pooled analyses.)

Number of Published HuGE Papers*
2001-2004

- **Year**   **Prevalence** **Associations** **Interactions**

- 2001   308   2141   436

- 2002   349   2799   569

- 2003   323   3010   598

- 2004   368   3486   604

Search

The GDPInfo query tool allows you to define your search with a combination of genes, diseases/conditions, topics and other factors.

Basic Search | Advanced Search | Search Instructions | Home | About GDPInfo | Contact Us

Genes: Enter a gene(s) or select an item from the Gene Menu.

? Gene(s) [   ]   (**Gene Menu**)
Search gene through GDB

Current Selected Gene(s)   [MTHFR   ]   Indicate "And" or "Or" if more than one gene.
[Or ▾]

Disease/Conditions: Enter a disease/condition or select an item from the Disease Menu.

? Disease(s) [   ]   (**Disease/Condition Menu**)

Current Selected Disease(s)   [   ]   Indicate "And" or "Or" if more than one disease.
[Or ▾]

Environmental or Personal Factors: Enter a Factor or select an item from the Factor Menu.

? Factor(s) [   ]   (**Factor Menu**)

Current Selected Factor(s)   [   ]   Indicate "And" or "Or" if more than one factor.
[Or ▾]

File   Edit   View   Favorites   Tools   Help

← Back ▾   → ▾   ⊗   ▣   ⌂   🔍Search   🗐Favorites   🎬Media   ⊚ | 🗐▾   🖨   🖸 ▾   🗐

Address 🗐 http://www2a.cdc.gov/genomics/GDPQueryTool/frmQuerySumPage.asp?IO_strGeneSymbol=&IO_strGeneSymbolValue=MTHFR ▾   🔗Go   Links »

New Search

You have selected one or more choices below.

	Gene(s): **MTHFR**
And	**Factor(s):**
And	**Disease/Condition(s):**

Search Result   Sort By   ⦿ Title   ○ Year Published

Expand	Document Source	Record(s) Found
➕	**HuGE E-Journal**	**4**
➕	**Fact Sheet**	**1**
➕	**Genotype Prevalence Table**	*Expand for details*
➕	**HuGE Published Literature**	**602**
➕	**HuGE Review**	**3**
➕	**Online Presentation**	**1**
➕	**Other Reports and Publications**	**6**

New Search

This application is best viewed in Microsoft Internet Explorer 5 or greater or in Netscape 6 or greater.

🗐 Done   🖳 Local intranet

🏁Start | 🗐 🖉 🌐 ⬛ ⬛ 🅒 🅰 🃏 🕐 | 🖳 🖸 🅰 🖉 ✉ 🗐 ✉ 🗐 🗐 🗐 🗐 🗐 | 🔊◇v3🖳 8:12 AM

Gene: MTHFR (5,10-methylenetetrahydrofolate reductase (NADPH)) ▼

Click on a column to sort data   View: ☑ **Prevalence (%)** ☐ **95% Confide**

Study Location (Reference #)	Gender	Race Or Ethnicity	# Subjects Studied	g.677C>T/g.677C>T	g.677C>T/g.677C	g.677C/g.677C	g.1298A>C/g.1298A>C	g.1298A>C/g.1298.
Africa (#41)	NS	African, sub-Saharan	234	0	13.2	86.8	-1	-1
Zaire & Cameroon (#42)	NS	NS	67	0	10.4	89.6	-1	-1
South Africa (#75)	NS	Black	114	-1	-1	-1	4.4	34.2
Asia (#41)	NS	Asian	346	3.5	28.3	68.2	-1	-1
Japan (#45)	M	Japanese	129	10.9	54.3	34.9	-1	-1
Japan (#46)	NS	NS	419	12.2	51.1	36.8	-1	-1
Japan (#47)	M	NS	778	10.2	46.4	43.4	-1	-1
Japan (#48)	M	Japanese	325	10.2	42.8	47.1	-1	-1
Japan (#49)	F	NS	98	11.2	50	38.8	-1	-1
Japan (#50)	NS	NS	260	11.2	51.9	36.9	-1	-1
Japan (#51)	NS	NS	105	18.1	48.6	33.3	-1	-1
Japan (#52)	NS	NS	310	13.5	51	35.5	-1	-1
Japan (#53)	NS	NS	146	11.6	29.5	58.9	-1	-1
Japan (#78)	NS	NS	243	-1	-1	-1	3.7	30.9
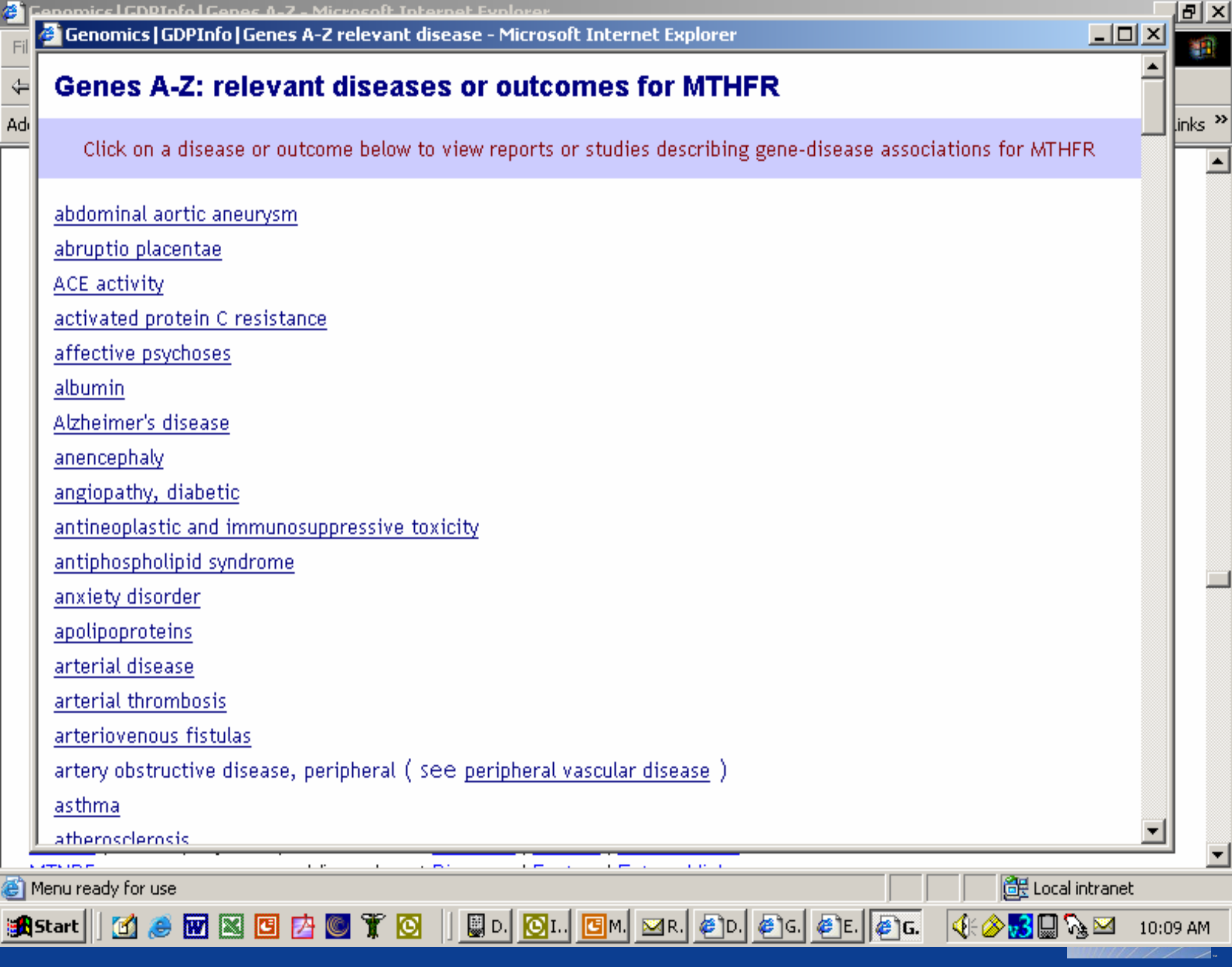
Genes A-Z: relevant diseases or outcomes for MTHFR

Click on a disease or outcome below to view reports or studies describing gene-disease associations for MTHFR

abdominal aortic aneurysm

abruptio placentae

ACE activity

activated protein C resistance

affective psychoses

albumin

Alzheimer's disease

anencephaly

angiopathy, diabetic

antineoplastic and immunosuppressive toxicity

antiphospholipid syndrome

anxiety disorder

apolipoproteins

arterial disease

arterial thrombosis

arteriovenous fistulas

artery obstructive disease, peripheral (see peripheral vascular disease)

asthma

atherosclerosis

File   Edit   View   Favorites   Tools   Help

⇐ Back ▾ ⇒ ▾ ⊗ ⟳ ⌂ | ⊗ Search ⟨★⟩ Favorites ⟨M⟩ Media ⟨⟩ | ⟨⟩▾ ⟨⟩ ⟨⟩ ▾ ⟨⟩

Address ⟨⟩ http://www2a.cdc.gov/genomics/GDPQueryTool/frmQueryBasicPage.asp   ▾   ⟨⟩ Go   Links »

Basic Search | **Advanced Search** | **Search Instructions** | **Home** | **About GDPInfo** | **Contact Us**

Genes: Enter a gene(s) or select an item from the Gene Menu.

? **Gene(s)**   [   ]   ⟨ **Gene Menu** ⟩
Search gene through GDB

Current Selected Gene(s) | MTHFR   ▲ | Indicate "And" or "Or"
| ▼ | if more than one gene.
                                      | Or ▾ |

Disease/Conditions: Enter a disease/condition or select an item from the Disease Menu.

? **Disease(s)**   [   ]   ⟨ **Disease/Condition Menu** ⟩

Current Selected Disease(s) | *ALL (Congenital anomalies)   ▲ | Indicate "And" or "Or"
| ▼ | if more than one disease.
                                      | Or ▾ |

Environmental or Personal Factors: Enter a Factor or select an item from the Factor Menu.

? **Factor(s)**   [   ]   ⟨ **Factor Menu** ⟩

Current Selected Factor(s) | ▲ | Indicate "And" or "Or"
| ▼ | if more than one factor.
                                      | Or ▾ |

? **Topic: Choose a topic category below. View definitions by rolling cursor over check boxes.**

⟨⟩ javascript:openDiseaseHierMenu()   ⟨⟩ Local intranet

⟨Start⟩ | ⟨⟩ ⟨⟩ ⟨W⟩ ⟨X⟩ ⟨⟩ ⟨⟩ ⟨⟩ ⟨⟩ ⟨⟩ | ⟨⟩ ⟨⟩ ⟨⟩ ⟨⟩ ⟨⟩ ⟨W⟩ ⟨⟩ ⟨⟩ ⟨⟩ ⟨⟩ ⟨⟩   ⟨⟩◇v3⊞⟨⟩   8:14 AM

File   Edit   View   Favorites   Tools   Help

Back   •   →   •   ⊗   ⟳   ⌂ | ⦿Search   ⭐Favorites   ⟐Media   ⦿ | ⧎▾ ⎙   ⬚ ▾ ⊟

Address ⧉ http://www2a.cdc.gov/genomics/GDPQueryTool/frmQuerySumPage.asp?IO_strGeneSymbol=&IO_strGeneSymbolValue=MTHFR ▾ | ⟿Go   Links »

GDPInfo Search

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New Search

You have selected one or more choices below.

Gene(s): MTHFR

And   **Factor(s):**

And   **Disease/Condition(s): *ALL (Congenital anomalies)**

| Search Result | Sort By ⦿ Title ○ Year Published |

Expand	Document Source	Record(s) Found
⊕	HuGE Published Literature	45
⊕	HuGE Review	1
⊕	Other Reports and Publications	3

New Search

⧉ Done   ⧉ Local intranet

Start | ... | 8:15 AM

CDC Home   Search   Health Topics A-Z

Genomics and Disease Prevention

SAFER · HEALTHIER · PEOPLE

Events   Training   Funding   Links   Search Genomics

HuGE Review

home > hugenet > reviews > MTHFR gene and congenital anomalies

5, 10-Methylenetetrahydrofolate reductase (*MTHFR*) Gene Variants and Congenital Anomalies
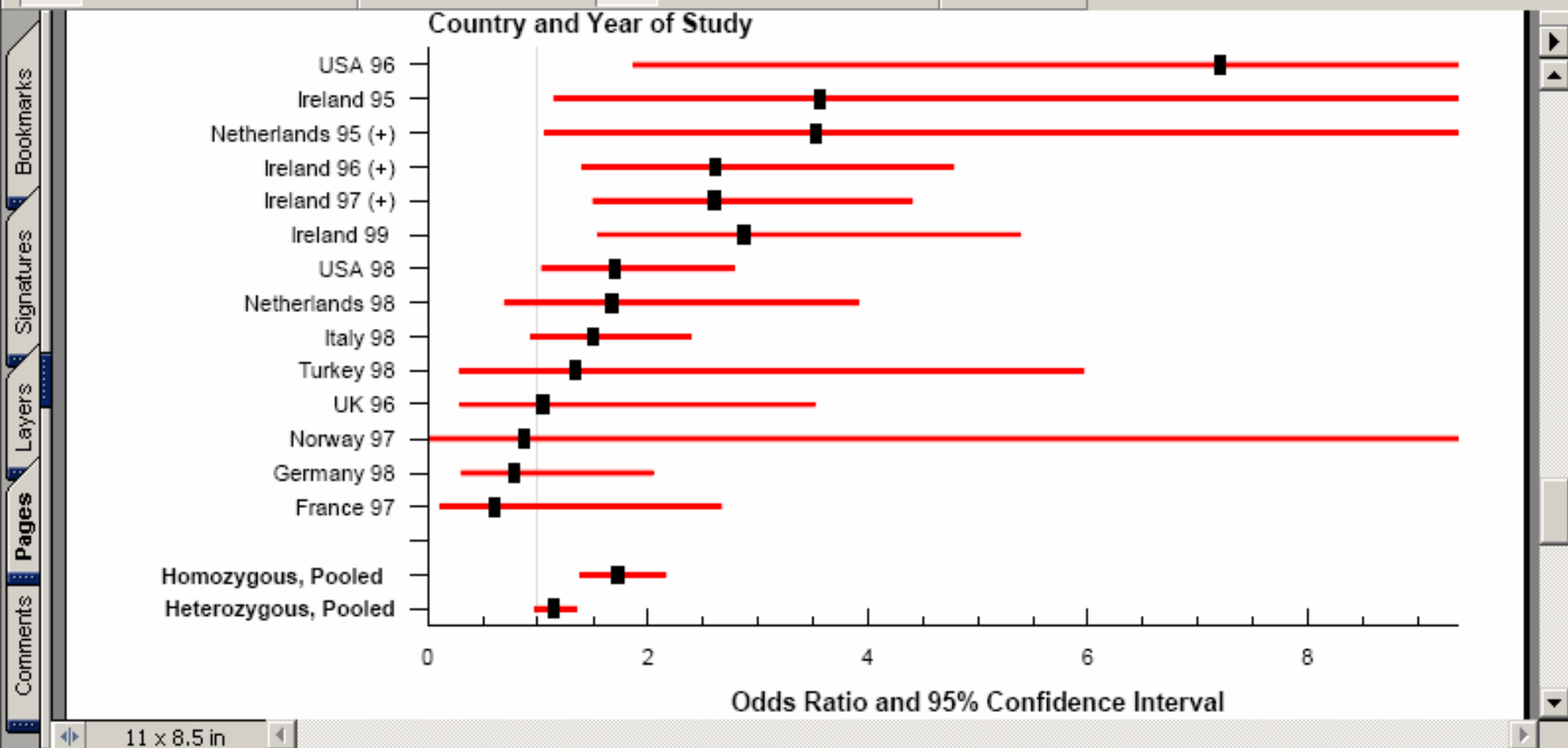
Lorenzo D. Botto and Quanhe Yang

Download print version

Authors' affiliations:

Centers for Disease Control and Prevention, National Center for Environmental Health, Division of Birth Defects and Pediatric Genetics, Atlanta, GA

August 16, 1999

Country and Year of Study

Odds Ratio and 95% Confidence Interval

HuGE Net Next Steps

- Knowledge base development
  - Develop tools for synthesis ("Cochrane" manual)
  - Develop research agenda and Pilot projects
- Enhance collaborations and information Sharing
  - **"Network of Networks"**
  - **Collaboration with Biobanks**
- Training and technical assistance
- Electronic journal (forum for negative studies)
- Use in public health genetics policy and practice

CDC

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Primary HuGE Research
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(case-control,
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Identify
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Research Priorities

HuGE Net

Analysis: G-G, G-E

Interpretation
Causal inference
Risk estimation

HuGE Journal

Synthesis
HuGE
Meta-analysis

Policy &
Practice

Appraisal
(Single study)

Dissemination